Real World Evidence: From Efficacy to Effectiveness

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Overview

• What is RWD
• Comparison of RWD vs RCT
• Examples of RW studies
• Strengths of RWE
Levels of evidence for therapy

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Systematic review (with homogeneity) of RCTs</td>
</tr>
<tr>
<td>1B</td>
<td>Individual RCT with narrow confidence interval</td>
</tr>
<tr>
<td>2A</td>
<td>Systematic review (with homogeneity) of cohort studies</td>
</tr>
<tr>
<td>2B</td>
<td>Individual cohort study</td>
</tr>
<tr>
<td>3</td>
<td>Individual case–control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series (and poor-quality cohort and case–control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial
Real-world data

“Data that are collected outside the controlled constraints of conventional randomised clinical trials to evaluate what is happening in normal clinical practice” ¹

Ever-increasing role in decisions that affect patients’ access to therapies²

Randomised controlled trials
Can it work?³

Real-world data
Does it work?³

## RCT data vs. Real World data

<table>
<thead>
<tr>
<th></th>
<th>RCTs</th>
<th>Real World Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Trial</strong></td>
<td>Experimental / interventional</td>
<td>Observational / non-intervention</td>
</tr>
<tr>
<td><strong>Primary focus</strong></td>
<td>Efficacy, safety, quality and cost-effectiveness</td>
<td>Effectiveness, safety, quality, cost-effectiveness, natural history, compliance and adherence, service models, patient preference</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>Narrow, restricted and motivated</td>
<td>Diverse, large and unrestricted</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Intense (ICH-GCP compliant)</td>
<td>Not required (?)</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>Gold standard / placebo</td>
<td>None / standard clinical practice / multiple iterations</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Clear sequence</td>
<td>Wide range</td>
</tr>
<tr>
<td><strong>Data collection confounders</strong></td>
<td>Standardised, controlled</td>
<td>Routine, recruitment bias (?)</td>
</tr>
<tr>
<td><strong>Validity</strong></td>
<td>Internal</td>
<td>External</td>
</tr>
<tr>
<td><strong>Randomisation &amp; Blinding</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Short (?)</td>
<td>Long</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$$ $$ $$ $$</td>
<td>$</td>
</tr>
</tbody>
</table>
Diverse and complex patients are present in clinical practice:

- Smoker
- Older age
- Obesity
- CVD
- Impaired renal function
- Multiple treatments
- High BP
- Cultural factors
- Retinopathy
Multimorbidity: Comorbidity of top 10 common conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage who only have the row condition*</th>
<th>Mean No of conditions in people aged &lt;65 years with row condition</th>
<th>Mean No of conditions in people aged ≥65 years with row condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>8.8</td>
<td>3.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.9</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.8</td>
<td>3.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Stroke/transient ischaemic attack</td>
<td>6.0</td>
<td>3.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6.5</td>
<td>3.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.6</td>
<td>2.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>14.3</td>
<td>2.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Painful condition</td>
<td>12.7</td>
<td>3.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Depression</td>
<td>25.4</td>
<td>2.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Dementia</td>
<td>5.3</td>
<td>4.1</td>
<td>4.6</td>
</tr>
</tbody>
</table>

* Percentage who do not have one of 39 other conditions in the full count

Guthrie B et al. *BMJ* 2012;345:e6341
Sources of real-world data

- **Patient registry**¹,²
  - Observational
  - Specified outcomes
  - Defined population

- **Practical clinical trial**¹,³
  - Prospective, randomised
  - Large, diverse population
  - Long follow-up

- **Electronic Health Record**¹
  - Disease-specific symptoms/treatments
  - Patient-level outcomes

- **Randomised controlled trial supplement**¹
  - Additional data collection
  - Resource utilisation
  - Patient-reported outcome

- **Health survey**¹
  - Health status
  - Healthcare utilisation
  - Treatment patterns

- **Claims database**¹
  - Administrative data
  - Diagnoses
  - Procedures
  - Costs

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Digitized Medical Information
Achievements of A1c in Europe: GUIDANCE Study

GUIDANCE study 7,597 patients with type 2 diabetes
Gap exists between checking HbA1c and achieving target HbA1c < 7.0%

GUIDANCE, Guideline Adherence to Enhance Care; HbA1c, glycated haemoglobin A1c.

results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic
Adverse effects of interventions: Real world vs RCT
19 studies, 58 meta-analysis

Meta-analyses of Adverse Effects Data Derived from Randomised Controlled Trials as Compared to Observational Studies: Methodological Overview

Su Golder¹*, Yoon K. Loke², Martin Bland³
1 Centre for Reviews and Dissemination, University of York, York, United Kingdom, 2 School of Medicine, University of East Anglia, Norwich, United Kingdom, 3 Department of Health Sciences, University of York, York, United Kingdom

Conclusions: …no difference on average in the risk estimate of adverse effects of an intervention derived from meta-analyses of RCTs and meta-analyses of observational studies

…it may be preferable for systematic reviewers to evaluate a broad range of studies

Golder S et al. PLOS Medicine 2011:8:e1001026
Real-world safety data

- RCTs may miss rare or slow-developing adverse events owing to limited patient numbers and duration

- Long-term surveillance in large numbers of patients, including groups unrepresented in RCTs is necessary to detect rare events

- Many types of real-world study provide safety data, including registries, claims databases and long-term observational studies

**RCT**, randomised controlled trial

Metformin use in people with heart failure

- Uncertainty on best management approaches to HF management
- HF patients excluded from trials
- Metformin Contraindicated in HF – due to potential risk of lactic acidosis
- Based on observational studies, FDA asked for warning to be removed in 2007 (Inzucchi et al Diabetes Care. 2007;30:e129)

Systematic reviews of observational studies:
Pooled adjusted risk ratios for metformin compared with other treatments for all-cause mortality

### Influence of Severe Hypoglycemia on Events in ADVANCE

<table>
<thead>
<tr>
<th>Events</th>
<th>Sv. Hypo: Yes (n=231)</th>
<th>Sv. Hypo: No (n=10909)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major macrovascular events</strong></td>
<td>33 (15.9%)</td>
<td>1114 (10.2%)</td>
<td>3.53 (2.41–5.17)</td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major microvascular events</strong></td>
<td>24 (11.5%)</td>
<td>1107 (10.1%)</td>
<td>2.19 (1.40–3.45)</td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause deaths</strong></td>
<td>45 (19.5%)</td>
<td>986 (9.0%)</td>
<td>3.27 (2.29–4.65)</td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CVD deaths</strong></td>
<td>22 (9.5%)</td>
<td>520 (4.8%)</td>
<td>3.79 (2.36–6.08)</td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-CVD deaths</strong></td>
<td>23 (10.0%)</td>
<td>466 (4.3%)</td>
<td>2.80 (1.64–4.79)</td>
</tr>
<tr>
<td>Adjusted model</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Incidence of CVD and mortality in patients experiencing hypoglycaemia

Data are unadjusted incidence rates

CV, cardiovascular; CVD, cardiovascular disease

## Time from hypoglycaemia to first CV event or death

<table>
<thead>
<tr>
<th></th>
<th>T1D</th>
<th>T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with hypoglycaemia and ≥1 CV event (n)</td>
<td>38</td>
<td>97</td>
</tr>
<tr>
<td>Time from first hypoglycaemic episode to first CV event (years)</td>
<td>1.5 (0.5; 3.5)</td>
<td>1.5 (0.5; 3.0)</td>
</tr>
<tr>
<td>Patients with hypoglycaemia and death (n)</td>
<td>169</td>
<td>493</td>
</tr>
<tr>
<td>Time from first hypoglycaemic episode to death (years)</td>
<td>1.1 (0.3; 2.3)</td>
<td>0.8 (0.3; 2.3)</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) from CPRD plus HES data.

CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics.

Prospective vs Retrospective data
Inclusion criteria
T1DM and T2DM
Treated with insulin for more than 12 months
Adult > 18 years
Informed consent to participate

Exclusion criteria
Non-ambulatory patients
Illiterate patients
Patients unable to complete written survey

SH, severe hypoglycaemia; NSH, non-severe hypoglycaemia; SAQ, self-assessment questionnaire
HAT: retrospective and prospective hypoglycaemia rates in T2D

Any and nocturnal based on 4 week period. †Retrospective data based on 6 month period; ‡Prospective data based on 4 week period; IRR, incidence rate ratio; IRR calculated from completers analysis set, incidence and prevalence calculated from full analysis set.

Khunti et al. Diab Obes Met 2016
ABCD nationwide liraglutide and exenatide audits: UK

- Two audits of liraglutide and exenatide real clinical use in the UK

**Exenatide audit**¹
- Launched December 2008
- Prospective database
- Routine measurements (non-interventional)
- The audit collected anonymised data on 6717 patients (2007 to 2009) submitted by 315 contributors from 126 centres

**Liraglutide audit**²
- Launched autumn 2009
- Prospective database
- Routine measurements (non-interventional)
- March 2013 status: 5948 patients from 89 centres

ABCD, Association of British Clinical Diabetologists; ALT, alanine aminotransferase; CV, cardiovascular; HbA₁₀₀, glycosylated haemoglobin

Real-world effects of liraglutide on $\text{HbA}_1\text{c}$ and body weight

BMI, body mass index

Effect of background diabetes therapy on HbA$_1c$ reduction

Data on adjusted mean (SE) and ED were analysed by ANCOVA with baseline HbA$_1c$ as a co-variate.
ANCOVA, analysis of covariance; CI, confidence interval; ED, estimated differences; HbA$_1c$, glycosylated haemoglobin; OADs, oral anti-diabetic drugs; SE, standard error.
Effect of diabetes duration on HbA$_{1c}$ reduction

Data on adjusted mean (SE) and ED were analysed by ANCOVA with baseline HbA$_{1c}$ as a co-variate. ANCOVA, analysis of covariance; CI, confidence interval; ED, estimated differences; HbA$_{1c}$, glycosylated haemoglobin; SE, standard error. Thong et al. Diabetes 2012;61(Suppl 1):A266.
ADA/EASD: position statement for managing hyperglycaemia

Healthy eating, weight control, increased physical activity

**Initial monotherapy**

- Metformin

**Two-drug combinations**

- **SU**
  - TZD DPP-4i SGLT2i GLP-1 RA Insulin
  - SU DPP-4i SGLT2i GLP-1 RA Insulin

- **TZD**
  - DPP-4i SGLT2i Insulin

- **DPP-4i**
  - SGLT2i Insulin

- **SGLT2i**
  - GLP-1 RA Insulin

**Three-drug combinations**

- **SU TZD**
  - DPP-4i Insulin

- **TZD**
  - DPP-4i SGLT2i GLP-1 RA Insulin

**More complex strategies**

- Insulin (MDI)

**Escalate therapy at 3 months if target not achieved.**

DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MDI, multiple daily injection; SU, sulfonylurea; TZD, thiazolidinedione.

Longitudinal HbA1c changes in patients on GLP1-RA

-1.15%

Earlier intensification by 6 months is associated with 18% higher odds of lowering HbA1c below 7% at 24 months

Montvida O et al. Diab Obes Met 2016 (online)

66,583 patients
Mean age 56 years
87% Obese
Longitudinal HbA1c changes

Delays in recognising glycaemic failure (therapeutic inertia)

Montvida O et al. Diab Obes Met 2016
Early Glycemic Control May Predict Persistence of Glycemic Control

- In the ACCORD trial, strict glycemic control (target HbA1c <6.0%) was initially targeted
- Patients were then transitioned to a target HbA1c of 7.0–7.9%, and followed for an additional 1.1 ± 0.2 years
- Patients with lower pre-transition HbA1c were more likely to maintain an HbA1c <6.5% over time

**Unadjusted**

<table>
<thead>
<tr>
<th>Pre-transition HbA1c (%)</th>
<th>RR (95% CI) of achieving a final HbA1c &lt;6.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5.5</td>
<td>Increased likelihood (RR) of achieving a final HbA1c &lt;6.5%</td>
</tr>
<tr>
<td>6.0–6.4</td>
<td>Decreased likelihood (RR) of achieving a final HbA1c &lt;6.5%</td>
</tr>
<tr>
<td>6.5–7.4</td>
<td>Decreased likelihood (RR) of achieving a final HbA1c &lt;6.5%</td>
</tr>
<tr>
<td>≥7.5</td>
<td>Decreased likelihood (RR) of achieving a final HbA1c &lt;6.5%</td>
</tr>
</tbody>
</table>

- Adjusted for demographics, co-interventions, baseline pre-randomisation HbA1c, BMI, and medications, and post-transition change in BMI and medications
- BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; RR, relative risk
Percentage of patients at HbA$_{1c}$ target (≤7.0%) at 3 and 24 months post index

40,627 patients, 5 European countries and US
Patients initiating Basal Insulin

Mauricio D et al. Diab Obes Metabol 2017 (online)
Failure to achieve target at 3 months associated with increased odds of not achieving target at 24 months

<table>
<thead>
<tr>
<th>Country</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>5.04</td>
<td>3.53–7.18</td>
</tr>
<tr>
<td>Germany</td>
<td>3.71</td>
<td>2.84–4.85</td>
</tr>
<tr>
<td>Italy</td>
<td>5.22</td>
<td>3.19–8.52</td>
</tr>
<tr>
<td>Spain</td>
<td>3.50</td>
<td>1.85–6.62</td>
</tr>
<tr>
<td>UK</td>
<td>5.51</td>
<td>3.73–8.13</td>
</tr>
<tr>
<td>USA</td>
<td>3.51</td>
<td>3.21–3.84</td>
</tr>
<tr>
<td>Overall</td>
<td>3.70</td>
<td>3.41–4.00</td>
</tr>
</tbody>
</table>

Mauricio D et al. Diab Obes Metabol 2017 (online)
Consequences of delayed intervention

At 5.3 years, significantly increased risk of:
- MI 67% (CI 39–101%)
- Stroke 51% (CI 25–83%)
- HF 64% (CI 40–91%)
- Composite CVE 62% (CI 46–80%)

CVE, cardiovascular endpoint; HF, heart failure; IT, treatment intensification; MI, myocardial infarction

Summary and conclusions

- Well-designed real-world studies complement RCTs
- Need to be aware of types of real world data
- Choose appropriate data and methodology to answer the question
- Need to be aware of strengths and limitations
Thank you

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